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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/676,873	09/30/2003	John Chan	COTH-P01-002	7993

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EXAMINER	
DEJONG, ERIC S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 06/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/676,873	CHAN ET AL.	
	Examiner	Art Unit	
	Eric S. DeJong	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-68* is/are pending in the application.

4a) Of the above claim(s) *2,17-20,36-55 and 57-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-16, 21-35, and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Specification

The objection to the disclosure for containing an embedded hyperlink and/or other form of browser-executable code is withdrawn in view of amendments to the specification filed by applicants on 04/17/2006.

The objection to the disclosure for failing to comply with the requirements of CFR § 1.821 through 1.825 regarding sequence disclosures is withdrawn in view of amendments to the specification filed by applicants on 04/17/2006.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 3-16, 21-35, and 56 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

In regards to claims 1, 3-16, 21-35, and 56, the instant claims are drawn to methods of engineering a spatially conserved catalytic motif into a recipient polypeptide that encompasses *in silico* computational embodiments. Said computational embodiments are non-statutory unless the claims include a step of physical transformation, or if the claims include a useful, tangible and concrete result. It is important to note, that the claims themselves must include a physical transformation

step or an useful, tangible and concrete result in order for the claimed invention to be statutory. It is not sufficient that a physical transformation step or a useful, tangible, and concrete result be asserted in the specification for the claims to be statutory. In the instant claims, there is no step of physical transformation, thus the Examiner must determine if the instant claims include a useful, tangible, and concrete result.

In determining if the instant claims are useful, tangible, and concrete, the Examiner must determine each standard individually. For a claim to be "useful," the claim must produce a result that is specific, substantial, and credible. For a claim to be "tangible," the claim must set forth a practical application of the invention that produces a real-world result. For a claim to be "concrete," the process must have a result that can be substantially repeatable or the process must substantially produce the same result again. Furthermore, the claim must recite a useful, tangible, and concrete result in the claim itself, and the claim must be limited only to statutory embodiments. Thus, if the claim is broader than the statutory embodiments of the claim, the Examiner must reject the claim as non-statutory.

The instant claims do not include any tangible result. A tangible result requires that the claims must set forth a practical application of the method so as to produce a real-world result. The instant claims recite method steps drawn to obtaining a spatial relationship for a first set of amino acid residues in a spatially conserved catalytic motif, identifying a second set of amino acid residues in the recipient polypeptide, and substituting said second set of amino acid residues with the first set of amino acid residues. However, these steps only suggest that the steps of obtaining, identifying, and

substituting amino acid residues take place in an *in silico* embodiment. The instant claims do no require that a physical transformation take place, such as the actual synthesis of a resultant engineered polypeptide. Further the instant claims do not require the communication of a tangible result to a practitioner of the claimed method, for example by displaying a resultant engineered polypeptide. As such, the instant claims are not limited to any tangible result.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-16, 21-35, and 56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In In re Wands (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the

invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to use the claimed invention one of skill in the art must be able to computationally modify a recipient polypeptide that binds a target by replacing an identified set of amino acid residues within said polypeptide with an identified spatially conserved catalytic motif, such that the engineered polypeptide would retain both of said binding and catalytic activities. For reasons discussed below, there would be an unpredictable amount of experimentation required to practice the claimed invention.

b) The disclosure provides methods and procedures for carrying out the *in silico* modeling of a recipient polypeptide to contain a spatially conserved catalytic motif. The disclosure does not provide detailed guidance on how to reliably determine when such computationally modeled polypeptides will retain both said binding and catalytic activities in a "real-world" engineered polypeptide other than relying on a brute force method of synthesizing and testing each modeled polypeptide in a laboratory environment.

c) The disclosure provides examples of computationally identifying catalytic sites that are suitable for engineering into a similar geometric region identified in a recipient polypeptide. The instant disclosure does not provide working examples wherein the computationally identified catalytic site was actually engineered recipient protein in the "real-world" and further tested to confirm that the resultant engineered polypeptide maintained the expected catalytic and binding activities as modeled.

d) The nature of the invention, computationally engineering polypeptide structures to obtain a new catalytically active polypeptide from readily available polypeptide and motif structures, is extremely complex.

e) The prior art shows that predicted structures can be used only if very close homologs with known structures are available. A recent review of protein modeling and structure prediction provided by Ginalski et al. published on states:

> "Theoretically, it should be possible to deduce structure from sequence by accurate simulation of physical processes. We are very far from achieving this goal, and the methods of practical importance were traditionally based on the observation that proteins with similar sequences are structurally similar as well." (Ginalski et al., page 1874, column 1, line 15 through column 2, line 5)

and

> "Predicted protein structures can be used if very close homologs with known structure are available... Currently available structure prediction methods do not allow for high-quality predictions of the quaternary structure of protein complexes and for the prediction of interactions between proteins. Current benchmarks indicate that methods predicting interactions can be successful mainly in cases when structures exhibit minimal conformation changes upon complex formation. Substantial errors observed in predicted models go beyond the limits tolerated by such methods." (Ginalski et al., page 1887 column 1, line 45 through column 2, line 2).

Claim 1 recites the method steps "a) obtaining a spatial relationship for the amino acid residues of a spatially conserved motif; b) identifying a set of amino acid residues in the recipient polypeptide, wherein said set of residues have a geometric relationship matches the spatially conserved geometry of the catalytic motif". Independent claims 21 and 56 recite similar steps wherein a conserved geometric motif is engineered replace a geometrically matched set of amino acids in a recipient polypeptide. However, the instant claims do not recite any limitation requiring a high degree of homology between

the catalytic motif and the replaced set of amino acids in a recipient polypeptide. In one embodiment, the catalytic domain engineered into a recipient polypeptide could interfere with the instantly claimed binding activity of said polypeptide. It is acknowledged that the catalytic motif is modeled so as to replace a set of amino acids with matching, spatially conserved geometry, however this does not provide for a high degree of sequence homology or functional homology. Similarly, the instant claims do not address the issue of reliably predicting if the modeled engineered polypeptide will maintain the predicted fold, overall structure, and said catalytic and binding activities when produced in a real-world laboratory environment.

f) The skill of those in the art of polypeptide modeling and structure prediction is extremely high.

g) The predictability of structural characteristics from comparative structural and geometric features is identified in the prior art only when very close homologs are utilized in the investigation.

h) The claims are broad in that they are drawn to engineering a generic recipient polypeptide to contain a generic spatially conserved catalytic motif.

The skilled practitioner would first turn to the instant disclosure for guidance in using the claimed invention. However, the disclosure lacks any evidence or guidance on how to reliably predict when a engineered polypeptide will maintain the predicted fold, overall structure, and said catalytic and binding activities when produced in a real-world laboratory environment. As such, the skilled practitioner would turn to the prior art for such guidance, however the prior art does not shows only examples where predicted

structures can be used only if very close homologs with known structures are available. Finally, said practitioner would turn to trial and error experimentation to determine if modeled structural characteristics for a given protein are present in empirically determined real-world protein structures. Such amounts to undue experimentation.

Claim Rejections - 35 USC § 112, Second Paragraph

The rejection of claims 1, 3-16, 21-35, and 56 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of arguments presented by applicants.

Regarding the breadth of claims, MPEP § 2173.04 states:

"Undue breadth of the claim may be addressed under different statutory provisions, depending on the reasons for concluding that the claim is too broad. If the claim is too broad because it does not set forth that which applicants regard as their invention as evidenced by statements outside of the application as filed, a rejection under 35 U.S.C. 112, second paragraph, would be appropriate."

Applicants state on page 17, lines 20-24 of the response filed 04/17/2006 that the scope of the claims is clear because the Examiner has correctly interpreted the claims to encompass all three recited embodiments. As such the claims have been construed to read on embodiments encompassing purely computational modeling, embodiments which encompass engineering a real-world polypeptide, and embodiments encompassing both *in silico* modeling techniques and generating a real-world polypeptide, as evidenced by applicants by statements outside of the application as filed.

Response to Arguments

Applicant's arguments filed 04/17/2006 have been fully considered but they are not persuasive.

In regards to the rejection of claims under 35 USC § 112, 1st paragraph, applicants argue that the Ginalski et al. comments regarding protein quaternary structure prediction is largely irrelevant with respect to claims 1 and 21, which are directed to embodiments with a single recipient polypeptide.

In response, it is noted that claim 1 is drawn a method of engineering a spatially conserved catalytic motif into a recipient polypeptide that binds a target. Claim 1 further specifies that the target is an extracellular signaling molecule with a K^D of 10^{-6} M or less. As such, the resultant engineered polypeptide is directly related to computational techniques of quaternary structures since the resultant polypeptide is intended to maintain a specified affinity for binding a target molecule. It is further noted that the disclosure of Ginalski et al. is a broad review of computational approaches directed to biomolecular structure prediction and is not restricted to a teachings regarding only quaternary structures.

Applicants further argue that Ginalski et al. supports the enablement of the claimed invention.

In response, it is noted that applicants argument does not specify any portion or teachings of Ginalksi et al. that would provide support for enablement of the claimed invention. As such applicants argument is not found persuasive.

Applicants further argue that the claimed invention partly relies on the replacement of only a limited number of amino acid residues in the recipient polypeptide.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the claims rely on only a limited number of amino acid residues) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). The instant claims recite steps drawn to replacing a first set of amino acid residues in a recipient protein with a second set of amino acid residues, however this does not provide any limit on the number of amino acid residues that are substituted. Further, applicants example (see page 16, lines 5-13) wherein only a single amino acid residue is replaced in a recipient scFv polypeptide is not within the scope of the instant claims as the claimed method requires that a plurality of amino acid residues within a first set are replaced a plurality of amino acid residues in a second set, i.e. a first set of amino acid residues is substituted with a second set of amino acid residues. Further, the claims are not limited to an equivalent one to one exchange of existing amino acids with replacement amino acids, as the number of amino acids in the first set are not required by the instant claims to be equal to the number of replacement amino acid residues in the second set.

Applicants further argue that the spatially conserved amino acids are usually, but not necessarily, non-consecutive amino acids, and as such the impact of each substitution is expected to be relatively independent at least compared to the impact of replacing a stretch of consecutive amino acids. Applicants further argue that multiple rotamers are usually available for each residues to be substituted, and thus minor classes with other recipient polypeptide atoms may be avoided by choosing the right rotamer.

In response, it is first noted that the features upon which applicant relies (i.e., consecutive versus non-consecutive amino acid replacement and choosing the right rotamer conformation) are not recited in the rejected claims. The instant claims are silent as to any ordering of the existing polypeptide amino acid residues which are to be replaced as well as the ordering of the replacement amino acid residues. It is further reiterated from the above rejection that the predictability of structural characteristics from comparative structural and geometric features is identified by the prior art only when very close homologs are utilized in a structural investigation. The instant claims do not address the issue of reliably predicting if the modeled engineered polypeptide will maintain the predicted fold, overall structure, and said catalytic and binding activities when a real-world polypeptide is actually synthesized. The instant disclosure does not provide any guidance to one of skill in the art regarding how to select amino acid substitutions that do not impact local structure nor does it teach how to avoid steric clashes by "choosing the right rotamer". As such, applicants arguments do not resolve the lack of enablement issue wherein a practitioner of the claimed invention would have

to turn to trial and error experimentation to determine if an engineered polypeptide will actually have the predicted structure and functional characteristics when the real-world equivalent is synthesized.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

20 June 2006
JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER

EDJ